

REMARKS

Reconsideration is respectfully requested in view of the remarks which follow.

The claims presently pending in the subject application are 26 – 43 and 47 – 49.

Claims 26 – 43 and 47 – 49 have been finally rejected under 35 USC § 103(a) over the combination of Alt, U.S. 5,512,684 in view of Gandolfi et al (US 4,999,362) and in view of Dorwald (*Side Reactions in Organic Synthesis, 2005, Wiley-VCH, page 2*). This rejection is respectfully traversed.

The claimed invention recites a process suitable for the bulk manufacturing of raloxifene hydrochloride in a pure and crystalline form, the process being simplified compared to those known in the prior art. The instantly claimed process is distinguishable over and differs from Alt US '684, the primary reference, in the features recited in steps d1) and d2), namely:

-the compound 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]- benzo[b]thiophene (I) free amine is not isolated after the hydrolysis with NaOH in MeOH, wherein the treatment of step d1) is conducted with a 30% excess of sodium hydroxide, while in Alt US '684 the *free amine (I) is isolated* after a very long procedure involving *solvent removal, extractions and chromatographic purification*;

-in the instant application the final product is the HCl salt of compound (I), while Alt's final product is a neutral form (free amine) of compound (I); specifically, d2) is further characterized by the fact that the acid used is concentrated HCl and step d2) is *done directly on the reaction mixture of d1)* to which equal weight amounts of water and ethyl acetate and, finally, 37% concentrated HCl are added,

Alt, US '684 is *completely silent about not isolating the free base* of compound (I) and, on the contrary, teaches that the work-up procedure after the basic hydrolysis is complicated and the purification procedure is even more time-consuming and cost ineffective. The Examiner still insists, however, and contrary to the evidence that this

difference is not crucial, but also insists further, that the combination with Dorwald anticipates step d1) and all the related features,

Specifically, the Examiner has affirmed that from the combined teachings of Alt and Dorwald would have suggested to one of ordinary skill in the art to reduce the number steps in order to achieve the desired product faster and in increased yield. The Examiner supports this affirmation by stating that Dorwald teaches that, *"in the design of an organic molecule, a synthetic chemist would need to analyze the shortest synthetic strategy which are most likely to give rapid access to the target compound, ideally in high yield and purity"*, thus allegedly rendering obvious step d1) and the features indicated therein.

First of all, it should again be highlighted, that the Examiner is continuing to make a trivial mistake by confusing the steps of a synthetic strategy with the steps of a single chemical reaction procedure. These are conceptually different and cannot be mixed-up.

Dorwald's teaching is related to the planning of a synthesis and the pathway along which to assemble the pieces to obtain a final compound. The pathway individuates the chemical intermediate which must be passed through. The synthesis design can be linear or convergent and in paragraph 1.2.1 it is clearly shown that usually a convergent synthesis is the shortest one. Dorwald's teaching to synthetic strategies is from a retrosynthetic point of view.

The shortest strategy, however, does not mean the omission of steps.

The shortest synthetic strategy as mentioned by Dorwald means that, among two or more possible pathways for the synthesis of a complex compound, one should choose the shortest one which involves the least number of intermediates and, therefore, the fewest number of chemical reactions.

Dorwald's teaching, however, is totally unrelated to chemical process development, to which, instead, the claimed invention relates. The development or optimization of a chemical process is definitely not the same as developing a synthetic strategy. A chemical process can be optimized only after that the synthetic strategy has

been chosen. The chemical process optimization focuses on the reaction conditions (reagents, time, temperatures, solvents, work up, purifications, etc.), while the synthetic strategy defines the chemical road for reaching the compound.

The distinguishing feature of the present invention is related to the optimization of a chemical process and, specifically, is related *to not isolating the free base* (as Alt teaches), but to transform it directly from the crude hydrolysis mixture into the HCl salt. This deals with the optimization of a chemical procedure within a single substep of a given synthetic pathway. This has nothing to do with the synthetic pathway. In fact, Alt and the instant invention describe different processes for the same synthetic pathway. All the more, with the difference being that Alt stops the synthesis at the free compound, while in the instantly claimed process Applicants go even beyond it to the HCl salt (which is not even disclosed by Alt).

By “*not isolating an intermediate*” does not mean that Applicants have reduced the number of steps of a synthetic strategy. “*Not isolating an intermediate*” is a matter of *chemical process optimization*. Not isolating an intermediate, in chemical development, is usually a risky procedure because one of ordinary skill in the art would expect to obtain a *less pure product*.

Since Dorwald is silent about the process for synthesizing raloxifene (free base or HCl) and all the more so since the Dorwald teaching is so general and generic that it cannot be directly and unambiguously interpreted as providing a specific suggestion to omit (or to skip) the isolation of raloxifene free base. All the more, Dorwald suggests to look for the shortest path, not to reduce the steps within a given path.

There is, therefore, no clear, teaching, suggestion or motivation or even a hint, to one of ordinary skill in the art to combine the teaching of Dorwald with Alt because the general indication stated in Dorwald does not refer to the indicated specific of d1) and, as already explained, if combined, the combination would have resulted in a *reduced yield and a poorer purity*, which is contrary to what the invention teaches and in view of which the combination of references is clearly improper.

Furthermore, in view of Alt it would be expected that by omitting the isolation step of compound (I) free base, the final product HCl salt would have been less pure. In

fact, it is well known to every organic chemist that if an intermediate is not isolated at the end of a chemical reaction, then impurities can remain in the quenched crude reaction mixture, and such impurities are then brought forward in the following chemical transformations up to the final product. In fact, isolation of a product usually involves a series of operations (such as filtration, washing and drying) that somehow purify the isolated compound. An isolation step cannot be omitted *a priori* and, on the contrary, it is ***absolutely surprising*** and totally unexpected that it can be done without a loss of purity in the final product. The foregoing confirms the unobviousness of d1) with respect to the combination of Alt and Dorwald.

Regarding Gandolfi, the Examiner suggests its combination with Alt for finding a clear hint to step d2), relating to the formation of raloxifene HCl, instead of the free base of raloxifene.

Gandolfi is a general and generic teaching with respect to the preparation of salts of amine compounds. Gandolfi is **silent** about raloxifene HCl and is also **silent** in suggesting that an amine salt (raloxifene or other) could be prepared by adding to the strong base hydrolysis crude reaction mixture, containing the free base, equal amounts of H₂O and AcOEt and then adding 37% HCl, then followed by washing the obtained suspension with equal amounts of H₂O and AcOEt. The Examiner does not justify where these claimed features can be derived in the combination.

Not only is Gandolfi silent about all of these features of the claimed invention, but again it is not seen what the Examiner's justification is why Gandolfi should be combined with Alt which is not related to a salt, but which, in a clearly contrary manner, suggests the obtaining of a free amine in order to have high purity and high yields.

Gandolfi's teachings are, indeed, so general in nature that nothing can be deduced with any reasonable expectation of success, specifically with respect to raloxifene HCl. Applicants wish to draw the attention of the Examiner that a different general teaching in organic chemistry is that the hydrochloric salt of a tertiary aliphatic amine very often turns to be ***highly hygroscopic*** and, therefore, very difficult to handle properly and very often difficult to crystallize.

Conclusion

The (A) – (E) rationales set forth by the Examiner at page 7 of the Office Action as being supportive of his determination of obviousness in the sense of § 103(a) is simply not understood.

The Examiner is requested to point out to Applicants where in the combination of references he has relied upon, are steps d1) and d2) of claim 26 taught, suggested or deemed to provide motivation to one of ordinary skill to “not isolating the free base, but to transform it directly from the crude hydrolysis mixture into the HCl salt.”

It clearly does not come under rationale (A) since not isolating the free base is not taught and its direct transformation is not taught. The method employed by Applicants in d1) and d2) are not known from the art applied by the Examiner and the results achieved by Applicants are entirely unpredictable.

Rationale “B” is equally inapplicable since steps d1) and d2) do not amount to simple substitutions in view of the teachings of the art.

Rationale “C” is not in point since a known technique is not being used to improve a “*similar method*” in the “*same way*”. In fact Applicants’ are providing an improved method of making raloxifene in increased quantity and greater purity by the use of an entirely different method which is neither taught, suggested, motivated or even hinted at by the trilogy of teachings posited by the Examiner.

Rationale (D) is equally inapplicable since an unobvious technique is being used which departs from the teaching of the prior art and which yields a purity equal to 98%, which result is entirely unpredictable.

Rationale (E) completely misses the mark since it relies on the thesis “obvious to try”. Why would one of ordinary skill in the art choose to **not isolate the free base**, as taught by Alt, but to go completely contra to that teaching and, instead, to **transform it directly into an HCl salt from the crude hydrolysis mixture**. Such a choice by an organic chemist is entirely unobvious to try; in fact, it is the very quintessence of unobviousness to proceed in such a manner when one can **expect to meet with failure**.

As can be seen by the foregoing, the KSR analysis is a strong endorsement of the merit of Applicants arguments that the claimed invention is unobvious.

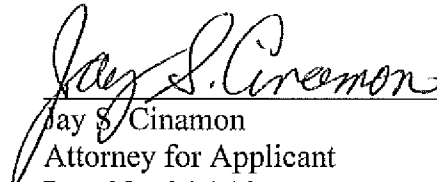
It is respectfully submitted that the claims distinguish over the combination of references since a case of *prima facie* obviousness has not been established by the Examiner by a preponderance of the evidence. The issuance of a Notice of Allowance is clearly in order and is respectfully solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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